

Grand challenges in rhinology

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Importance of Nasal Problems

The nose is our respiratory interface with the exterior world and, as such, bears the brunt of its challenges. The nasal and sinus epithelium, with its mucociliary clearance and production of nitric oxide gas, constitutes the first line of physical, chemical, and immunological defense of the airways, protecting us from the environment. Rhinitis and rhinosinusitis are universally experienced conditions, thanks to viral colds. This has led to trivialization of nasal symptoms and disease, even when persistent; however the realization that nasal disease is very costly to society, impairs sleep, quality of life, and work/school ability and that it is associated with a variety of co-morbidities involving the throat, lungs, sinuses, ears, and general well-being is gaining traction and leading to good quality research into etiology, prevention, and management. Many challenges remain into the etiology, pathophysiology, natural history, and therapy of upper respiratory tract disorders.

Allergic Rhinitis (AR)

AR is a highly prevalent global health problem, found in around a quarter of European populations ([1](#)). It has a significant negative impact on quality of life (QoL) of sufferers ([1](#) – [6](#)), reducing all areas of school and work performance ([7](#), [8](#)), impairing mood, cognitive, and driving ability ([9](#), [10](#)) probably *via* its effects on reduction of sleep quality ([11](#)).

Socioeconomic effects of AR are huge ([4](#), [5](#)). A recent survey in Sweden found an annual cost of €1.3 billion, mainly due to presenteeism ([12](#)). AR has a negative impact on work productivity greater than that of heart

disease and diabetes combined ([13](#)), hence the European Union prioritization of its control ([14](#)). In addition AR predisposes to new asthma and has deleterious effects upon existing asthma ([15](#)).

Treatment of AR is no longer simple as the disease has become more severe and complex in recent decades with many sufferers being polysensitized ([8](#), [16](#)) having moderate/severe disease ([1](#), [17](#), [18](#)) and persistent symptoms ([19](#)). Mixed forms of rhinitis have appeared, with a combination of allergic and non-allergic factors involved ([20](#)). In some countries local AR (i. e., localized nasal allergic response in the absence of systemic atopy, LAR) has been demonstrated ([21](#) - [23](#)). AR is among those conditions included in severe chronic upper airway disease (SCUAD, uncontrolled disease despite guideline-directed care) ([24](#), [25](#)) since, despite a plethora of available treatments and suitable guidelines ([26](#), [27](#)) AR often remains uncontrolled ([28](#)). The reasons for this are several, with patient, physician, disease, and treatment factors possibly involved. For such AR patients allergen immunotherapy may be an important treatment option ([29](#)). This more personalized treatment involves administering allergen extract, subcutaneously or sublingually, to desensitize patients, reducing both symptoms and medication requirements ([30](#)). Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have been shown to be effective in patients with seasonal and perennial AR in the real world as well as in clinical trials ([31](#)) and are recommended in guidelines ([29](#), [30](#)). Data suggests that immunotherapy for AR in children can prevent new sensitizations and disease progression to asthma ([31](#), [32](#)). Questions remain about the best formulations of allergens and as yet there is still a

search for biomarkers associated with, and predictive of, a successful response ([33](#), [34](#)).

The pathogenesis of AR is a classic example of allergic disease initiated by immunological sensitization to an allergen, probably initially in the nasal mucosa ([35](#)). The factors leading to this are both genetic and environmental, with the marked increase in AR prevalence over the last five decades probably relating to changes in the environment. Impairment of mucociliary clearance and increased epithelial permeability secondary to chemicals, pollutants, and biological factors probably allow access of molecules to the immune system, instead of their being swept away, swallowed and rendered harmless in the gut. Recent interest has also centered on the microbiome, following on from the hygiene hypothesis ([36](#), [37](#)). In the epidemiological ISAAC study ([38](#)) AR—associated factors, mostly shared with those of asthma and atopic dermatitis, were antibiotics, paracetamol, air pollution, farm animals in affluent countries, cats, and/or dogs, maternal, and paternal smoking, fast foods, vigorous physical activity in adolescents, frequent TV viewing, but not obesity. However, air pollution and passive smoking probably increase AR severity rather than contributing to its development ([39](#)) and few of the other associations have proven to be genuine risk factors ([40](#)).

Prevention of AR has proved difficult. There is some evidence for its reduction by exposure to farm animals in early life, and possibly to dogs, but results differ between developed and developing countries ([41](#) - [43](#)).

Probiotics and /or prebiotics failed to reduce AR when given pre and post-natally ([44](#), [45](#)).

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In recent years large scale data from mobile apps is revealing interesting facts, such as the separate nature of rhinitis with and without eye inflammation (rhinoconjunctivitis) and of rhinitis with multiple atopic co-morbidities, with involvement of different gene complexes in each of these ([46](#)).

Other areas of interest about which there is a need for more good data are non-allergic rhinitis and nasal hyperreactivity, both of which cause significant morbidity and quality of life impairment, whilst proving hard to treat effectively in many sufferers ([27](#) , [47](#)).

Rhinosinusitis, in which inflammation extends to the sinus linings, is also a highly prevalent, quality of life reducing, condition which can be acute or chronic. The latter, abbreviated as CRS, is a poly-phenotypic entity which has been extensively reviewed recently ([48](#)) with mention of research needs in this area. This includes management of CRS with and without nasal polyps, better, large randomized, controlled trials; real-life studies combining surgery plus medical treatment, the place of biologicals, management of uncontrolled disease, impact of the extent of surgery, identification of endotypes with particular management implications.

Links With Asthma

The concept of one airway one disease has become largely accepted—with the demonstration that most asthma patients have some form of upper airway disorder that can precede, affect and aid in classification of their lung disease ([15](#)). Rhinitis is associated with more asthma-related GP visits and hospital referrals, with associated higher costs, probably because it impairs

asthma control to a similar degree as does smoking ([49](#) - [51](#)). Effective AR and CRS treatment, both medical and surgical, can improve asthma control ([52](#) - [55](#)). Prevention of allergic asthma development by allergen immunotherapy to AR sufferers has been shown with both SCIT and SLIT ([31](#) , [32](#)), but not yet absolutely proven and the endotype for success with such therapy remains obscure.

The current requirements for asthma drug development mean that upper respiratory tract results in an asthma trial are rarely included in their major assessments- only the lower airway is monitored, whilst conversely separate upper respiratory tract studies done for nasal polyposis largely ignore asthma ([56](#) , [57](#)). In real life many subjects have both conditions- so it is to be hoped that real life monitoring of new drugs, particularly very expensive monoclonal antibodies, will cover the whole respiratory tract.

Surgery

For many years the upper respiratory tract has been the preserve of the ENT surgeon. Research efforts in this area tended to be sparse and of poor quality. This has changed with the advent of a new generation of scientifically trained surgeons with better investigative tools, including endoscopes and CT scans ([58](#)). The ease of access to the nose means that it has proved useful, *via* secretions, scrapings, and biopsies, in enhancing the understanding of mechanisms in the allergic and immune responses. Surgery as treatment for CRS is under investigation, with further studies ongoing ([59](#) , [60](#)).

Olfaction

Besides being a route for air entry and defense, the nose also provides us with the origins of the sense of smell, with cilia from olfactory receptors projecting from the brain through the cribriform plate of the skull and into the roof of the nose. Smell and its counterpart, flavor, is highly important to life and to well-being, but, like rhinitis, is often disregarded. Olfactory fibers radiate widely in the brain, particularly involving the limbic system, so smell is linked to memory and is highly emotive. Its loss can have marked impact causing feelings of isolation and reduced emotions. The resulting inability to form and maintain close personal relationships can lead to depression.

In recent years there has been increased awareness of olfaction. Olfactory receptors have been cloned and structurally assessed, leading to a Nobel prize for Linda Buck and Richard Axel ([61](#)). Development of the first of several validated tests ([62](#)) has allowed investigation of olfaction in various disorders and the demonstration of marked abnormalities in some neurodegenerative diseases ([63](#)). The olfactory pathway may represent a route for pathogens to ascend into the central nervous system (CNS) in diseases such as Parkinson's and Alzheimer's ([64](#)). Identification of malignancy or of impending epilepsy or diabetic coma by sniffing dogs has been reported ([65](#)). Most recently COVID-19 has highlighted the sense of smell. Anosmia can occur suddenly in COVID–19 sufferers ([66](#)) and may be different in several ways to that experienced in other viral upper respiratory tract infections. On current data more females and young people are being afflicted by coronavirus- induced smell loss which can be the only symptom

and in around 90% is transient, suggesting that inflammation and oedema in the olfactory cleft may be responsible, rather than receptor loss.

Conclusions

Clearly the upper airway is an area of promise for high quality research which could transform patients' lives. Thus, it forms part of the overall grand challenges in Allergy ([67](#)) which will be explored in *Frontiers in Allergy*.

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Conflict of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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